424 Rec'd PCT/PTO 25 JAN 2000

FORM PTO-1390 (REV 11-98) — U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

# TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

| ATTORNEY'S DOCKET NUMBER | US APPLICATION NO (If known, see 37 CFR 1 5) |
|---|---|
| 515-4183 | 09/463586 |

| INTERNATIONAL APPLICATION NO. | INTERNATIONAL FILING DATE | PRIORITY DATE CLAIMED |
|---|---|---|
| PCT/EP98/04567 | 21 July 1998 | 30 July 1997 |

TITLE OF INVENTION: PHARMACEUTICAL COMPOSITIONS CONTAINING VITAMIN D AND CALCIUM, THEIR PREPARATION AND THERAPEUTIC USE

APPLICANT(S) FOR DO/EO/US: Maurizio Valleri and Alessandro Tosetti

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S C. 371
3. [X] This express request to begin national examination procedures (35 U.S.C 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C 371(b) and PCT Articles 22 and 39(1).
4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [X] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [ ] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [ ] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

**Items 11. to 16. below concern document(s) or information included:**

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [X] Other items or information:

PCT Publication with Search Report and cited documents.
Report of the International Preliminary Examination Authority with annexes.
PCT Request
PCT Forms IB/308 and IB/332
PCT Form IB/306 of 22/04/99 and 23.11.99

CERTIFICATE OF MAILING BY "EXPRESS MAIL"

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I HEREBY CERTIFY THAT THIS PAPER OR FEE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE BY "EXPRESS MAIL POST OFFICE TO ADDRESSEE" SERVICE UNDER 37 CFR 1.10 ON THE DATE INDICATED ABOVE AND IS ADDRESSED TO BOX PCT, ASST. COMMISSIONER OF PATENTS, WASHINGTON, D.C. 20231

PRINTED NAME: JAMES V. COSTIGAN

SIGNATURE: 

420 Rec'd PCT/PTO 25 JAN 2000

| U.S. APPLICATION NO (if known, see 37 CFR 1.5) 09/463586 | INTERNATIONAL APPLICATION NO PCT/EP98/04567 | ATTORNEY'S DOCKET NUMBER 515-4183 |
|---|---|---|

17 [X] The following fees are submitted:

**BASIC NATIONAL FEE ( 37 CFR 1.492 (a) (1) - (5) ) :**

Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO ..... **$970.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO ..... **$840.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO ..... **$760.00**

International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) ..... **$670.00**

International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) ..... **$96.00**

| CALCULATIONS PTO USE ONLY | | |
|---|---|---|
| **ENTER APPROPRIATE BASIC FEE AMOUNT =** | $ 840.00 | |
| Surcharge of **$130.00** for furnishing the oath or declaration later than [X] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)). | $ 130.00 | |

| CLAIMS | NUMBER FILED | NUMBER EXTRA | RATE | | |
|---|---|---|---|---|---|
| Total claims | 18 - 20 = | 0 | X **$18.00** | $ 0 | |
| Independent claims | 1 - 3 = | 0 | X **$78.00** | $ 0 | |
| MULTIPLE DEPENDENT CLAIM(S) (if applicable) | | 0 | + **$260.00** | $ 0 | |
| **TOTAL OF ABOVE CALCULATIONS =** | | | | $ 970.00 | |
| Reduction of 1/2 for filing by small entity, if applicable. A Small Entity Statement must also by filed (Note 37 CFR 1.9, 1.27, 1.28). | | | | $ 0 | |
| **SUBTOTAL =** | | | | $ 970.00 | |
| Processing fee of **$130.00** for furnishing the English translation later than [ ]20 [ ]30 months from the earliest claimed priority date (37 CFR 1.492(f)). + | | | | $ | |
| **TOTAL NATIONAL FEE =** | | | | $ 970.00 | |
| Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property + | | | | $ 0 | |
| **TOTAL FEES ENCLOSED =** | | | | $ 970.00 | |
| | | | | **Amount to be: refunded** | $ |
| | | | | **charged** | $ |

a. [X] A check in the amount of $ 970.00 to cover the above fees is enclosed.

b. [ ] Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 08-1540. A duplicate copy of this sheet is enclosed.

**NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.**

SEND ALL CORRESPONDENCE TO
JAMES V. COSTIGAN, ESQ.
HEDMAN, GIBSON & COSTIGAN, P.C.
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NEW YORK, NY 10036-2646
212-302-8989

SIGNATURE

JAMES V. COSTIGAN
NAME

25,669
REGISTRATION NUMBER

Docket No.: 515-4183



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

| | | |
|---|---|---|
| In re Application of | ) | |
| | ) | |
| Maurizio Valeri et al | ) | Group Art Unit: |
| | ) | Examiner: |
| | ) | |
| Serial No.: not known | ) | |
| | ) | |
| Filed: not known | ) | |

For: PHARMACEUTICAL COMPOSITIONS CONTAINING VITAMIN D AND CALCIUM, THEIR PREPARATION AND THERAPEUTIC USE

New York, NY 10036
January 25, 2000

Assistant Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Sir:

This Amendment is being filed to reduce the filing fee of the above identified application. Kindly amend the subject application as follows:

IN THE CLAIMS

Kindly amend claims 3, 13 and 14 under the provisions of 37 CFR§1.121(a) by deleting the bracketed subject matter and inserting the underlined material;

3. (amended) Pharmaceutical composition according to Claim[s] 1 [and 2], in which the calcium salt is calcium phosphate.

13. (amended) Process for the preparation of a pharmaceutical composition according to Claim[s] 1 [and 7], characterized by the following steps:

a) In a granulator turning at high speed, distribut[e]ing the binding agent, consisting of propylene glycol or low molecular-weight polyethylene glycols over the calcium salt[.];

b) Adding the colloidal silica, approximately 25% of the mannite, the citric acid, and the sodium saccharin, and mixing

for the time required and at the appropriate speed[.]; c) Adding the mixture, prepared separately, consisting of sucrose palmitate, a suspending agent, flavoring, colouring agent, the remaining part of the mannite and the Vitamin $D_3$, and mixing together with the rest of the preparation[.]; and d) Distribut[e]ing the granulate thus obtained into bags.

14. (amended) Process for the preparation of a pharmaceutical composition according to Claim[s] 1 [and 8], characterized by the following steps:
a) In a granulator turning at high speed, [distribute] placing the binding agent, consisting of liquid parafin or silicon oil, over the calcium salt[.];
b) Adding in order, to a mixture of colloidal silica, carboxymethyl cellulose and sodium saccharin previously sifted, the Vitamin $D_3$ and the sorbitol, mixing thoroughly every time before a new ingredient is added [.] , and [P]pouring the mixture into the rotating granulator and mixing for the required time and at the appropriate speed[.]; and
c) Compressing the granulate to the required weight to obtain the desired tablets.

REMARKS

This Amendment is being filed to delete the multiple dependent claims and reduce the filing fee. It is requested that this Amendment be entered prior to calculating the filing fee.

Respectfully submitted,

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09/463586
Rec'd PCT/PTO 25 JAN 2000
PCT/EP98/04567

# PHARMACEUTICAL COMPOSITIONS CONTAINING VITAMIN D AND CALCIUM, THEIR PREPARATION AND THERAPEUTIC USE

## Scope of the invention

The present invention refers to pharmaceutical compositions containing Vitamin D and a calcium salt, the process for their preparation, and their use in the treatment of pathological forms involving loss of bone tissue in the elderly, such as osteoporosis, as well as in the prevention of illnesses linked to calcium metabolism in the elderly, such as those leading to fractures of the proximal femur or other non-vertebral fractures.

## State of the art

The use of Vitamin D and calcium salts, either separately or in association, for various illnesses, among which those concerning calcium metabolism in the elderly, is already well documented in the state of the art. For example, in FR 2724844, the existence of a therapeutic association is claimed between Vitamin D and calcium salts in combating osteoporosis.

However, the Vitamin D and calcium-based pharmaceutical formulations available today still present a number of problems which render them not altogether acceptable.

The problems that had to be faced for the pharmaceutical compositions that are the subject of the present invention were in particular:

a) the homogeneity of distribution of Vitamin $D_3$ in the final mixture;

b) the properties of flow of the powder of the calcium salt used; and, when present,

c) the rate of reconstitution of the suspension to be prepared as and when required.

In fact, for the preparation of these formulations, normally Vitamin D is used in the so-called "coated" form, since it presents greater stability than the pure crystalline form.

The "coated" form, however, presents the disadvantage of consisting of small granules that are highly dense and smooth, which renders their distribution inside the final mixture even more problematic, this distribution in itself already being complex on account of the small amount of the vitamin involved in comparison

with the other constituents of the pharmaceutical compositions that are the subject of the present patent.

In addition, the calcium salt used for this type of preparations normally undergoes a granulation process (either damp or dry) to overcome the problems due to the poor characteristics of flow that it presents in its most widely used form, i.e., in the form of fine powder, which makes it unsuitable for processing using ordinary high output rate machines. However, the granules (including those obtained with specific excipients for favouring disgregation) present a poor disgregation rate, which is instead highly desirable for the pharmaceutical preparation in bags, both in order to guarantee a good level of bio-availability and to obtain a suspension to be prepared as and when required, in which the salt may be finely divided in order to reduce the rate of sedimentation of the suspension and eliminate the "sand" effect which is noted when granular suspensions of this type are taken.

There is therefore an evident need to have available new pharmaceutical formulations containing a Vitamin D-calcium association which may enable a high dosage of calcium mixed in a homogenous way with very low doses of Vitamin D (for example 1-2 g of calcium for 500 - 1000 I.U. of Vitamin D), may present a good stability, may have a high level of bio-availability, may be suited to being processed using high-speed production machines, and may be pleasant to take for the patient.

**Detailed description of the invention**

The pharmaceutical composition according to the invention makes it possible to overcome the aforesaid problems owing to a "granulation" of the calcium salt, at the rate of 1 - 2 g of calcium for 500 - 1000 I.U. of vitamin D, in the presence of propylene glycol or a polyethylene glycol presenting a molecular weight comprised between 300 and 1500 (for formulations that involve subsequent disgregation in water) or (in the case of pharmaceutical formulations that do not envisage subsequent disgregation) with liquid paraffin or silicone oil.

Surprisingly, the addition of the calcium salt to the above said glycols makes it possible to obtain, a triple advantageous effect::

a) The even and diffused distribution of the glycol over the calcium granules, as well as over the other components of the formulation, plays a "binding" effect on

the small granules of coated Vitamin $D_3$. In this way, there is an anchoring of the particles of the vitamin to the system, thus enabling its even distribution ;

b) The atypical granulation of the calcium salt, taking place with this agent, modifies the properties of flow just enough to obtain a mixture having characteristics of smoothness such as to enable its processing with high output machines;

c) The aforesaid modification of the properties of flow of the calcium salt however is not an obstacle to its complete re-dispersion, where this is required, once the aqueous suspension has been reconstituted.

Moreover the moistening effect exerted by the propylene glycol on the calcium phosphate must be considered. This effect renders the operation of reconstitution of a dispersion faster than the one obtainable without its use.

According to the invention particularly preferred is propylene glycol. In this connection it is important to note that the well-known sour taste of propylene glycol or somewhat bitter one of low-molecular-weight polyethylene glycols may be easily covered by the common excipients and sweeteners, without affecting the pleasantness of the resultant pharmaceutical composition.

As binding agents for pharmaceutical forms that do not have to be dispersed in water, the substances that have proved extremely useful, and hence constitute a subject of the present invention, are liquid paraffin and silicone oil. These components in fact make it possible to obtain the same aggregating effect as the previous excipients and an equivalent distribution of the active principles.

Among the various forms of Vitamin D used for the formulations according to the invention, Vitamin $D_3$, Vitamin $D_2$ and their mixtures are preferred.

The calcium salt used for the present invention is, for example, chosen in the group consisting of: phosphate, glycerophosphate, carbonate, bicarbonate, lactate, citrate, tartrate, gluconate, and chloride.

Particularly preferred is calcium phosphate and, more particularly, tribasic phosphate.

Normally the quantity of calcium phosphate is comprised between 30 - 80% by weight calculated on the total composition.

The pharmaceutical compositions that form the subject of the present patent moreover comprise the usual moistening agents (e.g., sucrose palmitate); fluidifying agents (such as, colloidal silica); suspending agents (such as cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose); organoleptic correctors (such as, flavouring substances, citric acid); sweeteners (such as mannitol, sorbitol, saccharin salts, aspartame, etc.); and colouring agents (such as E110).

It must be noted that the pharmaceutical compositions according to the present invention are not suitable for dermatology applications (for example in the form of creams).

According to a preferred formulation (bags) the pharmaceutical composition of the present application contains the propylene or the polyethylene glycol in a quantity comprised between 5 - 15% by weight calculated on the total weight of the formulation.

Non-limiting examples of the present invention are the following:

Example 1

Lot for 6000 bags

The sucrose palmitate, citric acid and sodium saccharin are sifted using a sieve with 0.5-mm mesh.

The propylene glycol is distributed over the calcium phosphate in a high speed granulator by setting the following process parameters:

2 minutes with impeller at 80 r.p.m. and chopper turned off, followed by 2 minutes with impeller at 160 r.p.m. and chopper at 1500 r.p.m.

The colloidal silica, 25% of the mannite required, the citric acid, and the sodium saccharin are added to the mixture.

The above is mixed for 6 minutes with impeller at 80 r.p.m. and chopper at 1500 r.p.m. until a homogeneous composition is obtained.

Prepared separately, in a cube mixer at a rate of 25 r.p.m. for 15 minutes, is a premix consisting of sucrose palmitate, microcrystalline cellulose and carboxymethyl cellulose, lemon flavouring, E110, the remaining part of the mannite, and the Vitamin $D_3$.

The mixture thus obtained is transferred into the granulator and mixed with the rest of the preparation, according to the following parameters:

1 minute with impeller at 140 r.p.m. and chopper at 1500 r.p.m., followed by 30 seconds with impeller at 140 r.p.m. and chopper turned off.

The granulate thus obtained is distributed in the bags, which thus contain a preparation having the following composition:

| | |
|---|---|
| Tribasic calcium phosphate (corresponding to 1200 mg of $Ca^{++}$) | 3.100 g |
| Cholecalciferol (Vit. $D_3$) 100 000 IU/g (corresponding to 800 IU) | 0.008 g |
| Propylene glycol | 0.800 g |
| E110 | 0.002 g |
| Colloidal silica | 0.120 g |
| Lemon flavouring | 0.100 g |
| Microcrystalline cellulose - MCC | 0.200 g |
| Sodium saccharin | 0.015 g |
| Anhydrous citric acid | 0.165 g |
| Sucrose monopalmitate | 0.120 g |
| Mannitol q.s. to | 7.000 g |

In a similar way, but using polyethylene glycol instead of propylene glycol, bags may be prepared containing a preparation having the following composition:

| | |
|---|---|
| Tribasic calcium phosphate (corresponding to 1200 mg of $Ca^{++}$) | 3.100 g |
| Cholecalciferol (Vit. $D_3$) 100 000 IU/g (corresponding to 800 IU) | 0.008 g |
| Polyethylene glycol 400 | 0.800 g |
| E110 | 0.002 g |
| Colloidal silica | 0.120 g |
| Lemon flavouring | 0.100 g |
| Microcrystalline cellulose - MCC | 0.200 g |
| Sodium saccharin | 0.015 g |
| Anhydrous citric acid | 0.165 g |
| Sucrose monopalmitate | 0.120 g |
| Mannitol q.s. to | 7.000 g |

Example 2 (tablets)

Preparation for 20,000 tablets

The liquid paraffin is distributed over the calcium phosphate in a high speed granulator, setting the following process parameters:

2 minutes with impeller at 80 r.p.m. and chopper turned off, followed by 2 minutes with impeller at 160 r.p.m. and chopper at 1500 r.p.m.

The colloidal silica, the carboxymethyl cellulose, the sodium saccharin and the orange flavouring are sifted using a sieve with a 0.5-mm mesh.

Vitamin $D_3$ is added to the above-mentioned components and the product is mixed using a cube mixer at a rate of 25 r.p.m. for 5 minutes.

The sorbitol is then added, and everything is mixed in the cube mixer for 10 minutes at 25 r.p.m.

This premix is transferred into the granulator and is mixed with the rest of the preparation, by setting the following process parameters:

1 minute with impeller at 140 r.p.m. and chopper at 1500 r.p.m., followed by 30 seconds with impeller at 140 r.p.m. and chopper turned off.

The granulate is compressed to the required weight to obtain tablets having the following composition:

| | |
|---|---|
| Tribasic calcium phosphate (corresponding to 1200 mg of $Ca^{++}$) | 3.100 g |
| Cholecalciferol (Vit. $D_3$) 100 000 IU/g (corresponding to 800 IU) | 0.008 g |
| Liquid paraffin | 0.500 g |
| Sodium carboxymethyl cellulose | 0.050 g |
| Sodium saccharin | 0.015 g |
| Orange flavouring | 0.100 g |
| Sorbitol q.s. to | 4.400 g |

In the same way, using silicone oil instead of liquid paraffin, it is possible to obtain tablets having the following composition:

| | |
|---|---|
| Tribasic calcium phosphate (corresponding to 1200 mg of $Ca^{++}$) | 3.100 g |
| Cholecalciferol (Vit. $D_3$) 100 000 IU/g | 0.008 g |

| | |
|---|---|
| (corresponding to 800 IU) | |
| Silicone oil | 0.500 g |
| Sodium carboxymethyl cellulose | 0.050 g |
| Sodium saccharin | 0.015 g |
| Orange flavouring | 0.100 g |
| Sorbitol q.s. to | 4.400 g |

The pharmaceutical compositions that form the subject of the present invention were made for the purpose of being used in the treatment of nutritional deficiency of calcium and Vitamin D in the elderly, to reduce the loss of bone tissue linked to age and to prevent proximal femur fractures and other non-vertebral fractures. These pharmaceutical compositions may be used also to prevent osteoporosis induced by chronic treatment with corticosteroids.

I.U. as used in the present application means International Units and corresponds to the amount having the activity of 0.0025 $\gamma$ of Vitamin D3.

## CLAIMS

1. Pharmaceutical composition containing as active principles Vitamin D associated to a calcium salt characterized in that it comprises a binding agent chosen in the group consisting of: propylene glycol, a polyethylene glycol presenting a molecular weight comprised between 300 and 1500, liquid paraffin or silicone oil and that the Vitamin D is present at the rate of 1 - 2 g of calcium for 500 1000 I.U. of Vitamin D.

2. Pharmaceutical composition according to Claim 1, in which the calcium used is in the form of a salt chosen in the group consisting of:
phosphate, glycerophosphate, carbonate, bicarbonate, lactate, citrate, tartrate, gluconate, and chloride.

3. Pharmaceutical composition according to Claims 1 and 2, in which the calcium salt is calcium phosphate.

4. Pharmaceutical composition according to Claim 3 wherein the calcium phosphate is 30 - 80% by weight calculated on the total composition.

5. Pharmaceutical composition according to Claim 1, in which the Vitamin D used is Vitamin $D_2$ (or ergocalciferol), Vitamin $D_3$ (or cholecalciferol), or one of their mixtures.

6. Pharmaceutical composition according to Claim 5, in which the vitamin used is Vitamin $D_3$.

7. Pharmaceutical composition (bag) according to Claim 1, containing the propylene glycol or polyethylene glycol in a quantity comprised between 5-15% by weight calculated on the total composition.

8. Pharmaceutical composition (tablet) according to Claim 1, containing liquid paraffin or silicone oil.

9. Pharmaceutical composition according to Claim 7, characterized as follows:

| | |
|---|---|
| Tribasic calcium phosphate | 3.100 g |
| (corresponding to 1200 mg of $Ca^{++}$) | |
| Cholecalciferol (Vit. $D_3$) 100 000 IU/g | 0.008 g |
| (corresponding to 800 IU) | |
| Propylene glycol | 0.800 g |
| E110 | 0.002 g |

| | | |
|---|---|---|
| Colloidal silica | 0.120 | g |
| Lemon flavouring | 0.100 | g |
| Microcrystalline cellulose - MCC | 0.200 | g |
| Sodium saccharin | 0.015 | g |
| Anhydrous citric acid | 0.165 | g |
| Sucrose monopalmitate | 0.120 | g |
| Mannitol q.s. to | 7.000 | g |

10. Pharmaceutical composition according to Claim 7, characterized as follows:

| | | |
|---|---|---|
| Tribasic calcium phosphate | 3.100 | g |
| (corresponding to 1200 mg of $Ca^{++}$) | | |
| Cholecalciferol (Vit. $D_3$) 100 000 IU/g | 0.008 | g |
| (corresponding to 800 IU) | | |
| Polyethylene glycol 400 | 0.800 | g |
| E110 | 0.002 | g |
| Colloidal silica | 0.120 | g |
| Lemon flavouring | 0.100 | g |
| Microcrystalline cellulose - MCC | 0.200 | g |
| Sodium saccharin | 0.015 | g |
| Anhydrous citric acid | 0.165 | g |
| Sucrose monopalmitate | 0.120 | g |
| Mannitol q.s. to | 7.000 | g |

11. Pharmaceutical composition according to Claim 8, characterized as follows:

| | | |
|---|---|---|
| Tribasic calcium phosphate | 3.100 | g |
| (corresponding to 1200 mg of $Ca^{++}$) | | |
| Cholecalciferol (Vit. $D_3$) 100 000 IU/g | 0.008 | g |
| (corresponding to 800 IU) | | |
| Liquid paraffin | 0.500 | g |
| Sodium carboxymethyl cellulose | 0.050 | g |
| Sodium saccharin | 0.015 | g |
| Orange flavouring | 0.100 | g |
| Sorbitol q.s. to | 4.400 | g |

12. Pharmaceutical composition according to Claim 8, characterized as follows:

| | |
|---|---|
| Tribasic calcium phosphate | 3.100 g |
| (corresponding to 1200 mg of $Ca^{++}$) | |
| Cholecalciferol (Vit. $D_3$) 100 000 IU/g | 0.008 g |
| (corresponding to 800 IU) | |
| Silicone oil | 0.500 g |
| Sodium carboxymethyl cellulose | 0.050 g |
| Sodium saccharin | 0.015 g |
| Orange flavouring | 0.100 g |
| Sorbitol q.s. to | 4.400 g |

13. Process for the preparation of a pharmaceutical composition according to Claims 1 and 7, characterized by the following steps:

a) In a granulator turning at high speed, distribute the binding agent, consisting of propylene glycol or low-molecular-weight polyethylene glycols over the calcium salt.

b) Add the colloidal silica, approximately 25% of the mannite, the citric acid, and the sodium saccharin, and mix for the time required and at the appropriate speed.

c) Add the mixture, prepared separately, consisting of sucrose palmitate, a suspending agent, flavouring, colouring agent, the remaining part of the mannite, and the Vitamin $D_3$, and mix together with the rest of the preparation.

d) Distribute the granulate thus obtained into bags.

14. Process for the preparation of a pharmaceutical composition according to Claims 1 and 8, characterized by the following steps:

a) In a granulator turning at high speed, distribute the binding agent, consisting of liquid paraffin or silicone oil, over the calcium salt.

b) Add in order, to a mixture of colloidal silica, carboxymethyl cellulose and sodium saccharin previously sifted, the Vitamin $D_3$ and the sorbitol, mixing thoroughly every time before a new ingredient is added. Pour the mixture into the rotating granulator and mix for the required time and at the appropriate speed.

c) Compress the granulate to the required weight to obtain the desired tablets.

15. Composition according to Claim 1, for use in the treatment of nutritional deficiency of calcium and Vitamin D in the elderly, to reduce the loss of bone

tissue linked to age and to prevent femoral fractures and other non-vertebral fractures.

16. Composition according to Claim 1, for use in the prevention of osteoporosis induced by treatment with corticosteroids.

17. Method for the treatment of nutritional deficiency of calcium and Vitamin D in the elderly, to reduce the loss of bone tissue linked to age and to prevent femoral fractures and other non-vertebral fractures, in which therapeutically effective quantities of a composition according to Claim 1 are administered to the patient.

18. Method according to Claim 16 for the prevention of osteoporosis induced by treatment with corticosteroids.

Docket No: 515-4183

APPLICATION FOR UNITED STATES LETTERS PATENT 09/463586
DECLARATION, POWER OF ATTORNEY, AND PETITION

24 APR 2000

As a below-named inventor, I declare that:

My residence, post office address and citizenship are as stated next to my name; I believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural inventors are named below) of the invention which is described and which is claimed in the specification, entitled: PHARMACEUTICAL COMPOSITIONS CONTAINING VITAMIN D AND CALCIUM, THEIR PREPARATION AND THERAPEUTIC USE

The specification [ ] is attached hereto [X] was filed on 25 Jan. 2000, as Application Serial No. 09/463,586.

[X] was filed as PCT international application
Number PCT/EP98/04567
on 21 July 1998
and was amended under PCT Article 19
on _____ (if applicable)

I hereby state that I have reviewed and understand the contents of said specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.[1]

| COUNTRY | APPLICATION NUMBER | DATE (Day, Month, Year) | PRIORITY CLAIMED UNDER 35 U.S.C. 119 |
|---|---|---|---|
| ITALY | FI97A000184 | 30 July 1997 | Yes [X] No [ ] |
| | | | Yes [ ] No [ ] |

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

[1] In Non-Convention cases, a listing of all filings and current status of cases filed more than a year before the U.S. filing is required to comply with 37 CFR 1.56(a). Such a listing may be attached.

| APPLICATION SERIAL NO. | FILING DATE | STATUS |
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I hereby appoint my attorneys with full power of substitution and revocation, to prosecute this application and to transact all business in the U.S. Patent & Trademark Office connected therewith:

Edward A. Hedman, Reg. No. 22,120; Thomas M. Gibson, Reg. No. 24,638; James V. Costigan, Reg. No. 25,669; Kenneth F. Florek, Reg. No. 33,173; Alan B. Clement, Reg. No. 34,563; Martin P. Endres, Reg. No. 35,498 and Timothy X. Gibson, Reg. No. 40,618.

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The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

| INVENTOR(S) | DATE | RESIDENCE AND P.O. ADDRESS |
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